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INTRODUCTION

Symposium on biochemical insight into the regulation of renal function

The kidney plays a central role in the maintenance of body fluid volume and composition. The maintenance is defined by the integration of glomerular filtration and tubular reabsorption of the secretion of water and electrolytes which are regulated by hemodynamic, neural, and hormonal control. In addition, the kidney is a source of various hormones, some of which modulate renal function as a local hormone. The physiological complexity of the functional integrity of the kidney has been clarified much over the past decade or so due to the development and availability of highly sophisticated techniques such as micropuncture and in vitro perfusion of isolated nephron segments. These techniques have furthered insight into the physiological function of defined nephron segments which are distinct in their morphological and metabolic properties.

The manner in which physiological transport characteristics of the nephron are mutually coupled and regulated by cellular metabolic and biochemical events has been an intense interest of many investigators. Conventional biochemical analyses of renal function have focused mainly on biochemical and enzyme reactions which occur in the kidney. Such approaches may not have been initially directed to clarify the regulation and coupling of tubular transport function with cellular metabolism. Advancement in biochemical techniques has allowed clarification of the distribution of certain biochemical reactions along the nephron by analyzing the presence of specific metabolic reactions and/or enzyme activities in the defined nephron segments. Nonetheless, how such metabolic and biochemical reactions are coupled to tubular transport function has been poorly understood.

This Symposium attempts to provide state-of-the-art discussions of the latest research concerning the regulation of renal function from biochemical and biophysical viewpoints. Such discussions may further our understanding of the biochemical events intimately related to the tubular transport function. Because there is a distinct difference in the transport function in each nephron segment, that is, nephron heterogeneity, contributors were asked to present their respective subjects to relate to the physiological function of the kidney and nephron heterogeneity. They were encouraged to present their own biased or unbiased viewpoints based on their own experiments rather than to present a comprehensive review on the topic which could be found elsewhere in recent publications [1–3].

Because a major task of the kidney is to transport sodium and its accompanying ions which are energized primarily or secondarily by ATP via Na,K-ATPase localized in the basolateral plasma membrane, this topic appears first. Dr. Lazaro J. Mandel presents his own work involving separated proximal tubule preparations on the relationship between oxygen consumption and ATP turnover which drive primary active sodium transport. He explains how the rate of ATP production by oxidative phosphorylation in the mitochondria and ATP consumption by sodium transport by Na,K-ATPase in the plasma membrane are coupled. This article is followed by an overview on the molecular structure, function, and regulation of Na,K-ATPase by Dr. Peter L. Jørgensen. The readers cannot help but be impressed by the fine structural organization of the Na,K-ATPase protein and translocation of cations by the enzyme across the plasma membranes.

Also, there are ATPases other than Na,K-ATPase in the kidney. Dr. Adrian I. Katz first discusses the distribution of Na,K-ATPase along the nephron as well as its regulation and then discusses Ca-ATPase and proton ATPase in the kidney. His review clarifies that, in contrast to Na,K-ATPase and its relation to active sodium transport, much work is needed to understand the role of these latter two ATPases in the regulation of tubular Ca and proton transport.

The energy necessary to support the transport of sodium and other ions is derived primarily from oxidation of various substrates and from anaerobic glycolysis in the papilla. Dr. Julius J. Cohen and co-workers contribute to our understanding of the relationship between energy requirements for the support of sodium reabsorption and other renal work primarily utilizing functioning intact kidneys. He provides critical reviews on his and other data obtained using these techniques on the oxygen consumption, sodium reabsorption, and substrate utilization and oxidation, and points out the limitation of estimating the energy cost based on these measurements partly because of the complexity of the renal work requiring energy beside sodium transport, nephron heterogeneity, and substrate interconversion.

Dr. Cohen's article is followed by a brief review by Drs. Walter G. Guder, Siegfried Wagner, and Gabriele Wirthensohn on the presence of supremacy of substrate utilization in each nephron segment and interconversion of substrates. The presence of intricate interactions at the substrate level undoubtedly explains and supports some of Dr. Cohen's view.

The renal tubule epithelium in culture has become a powerful study tool directed to a variety of physiological and metabolic properties of the nephron. Dr. Michael F. Horster, a pioneer in this area of nephrology research, reviews the most recent developments in several aspects of nephron function utilizing cultured tubule cells. These developments relate to tubule cell growth, transport and metabolism by cultured tubule cells, and cell differentiation into polarized tubules.

The relationship between glucose and the kidney is another interesting subject of research. It has been clearly shown that the kidney produces glucose from noncarbohydrate precursors (gluconeogenesis). Glucose may be necessary to support transport, and glucose may serve as a substrate to produce energy for transport. These diverse relations between glucose and the

nephron function may occur in the same or different nephron segments. Accordingly, Drs. Brian D. Ross, Joseph Espinal, and Patricio Silva provide an up-to-date view on glucose metabolism and renal tubular function.

One of the most important metabolic reactions occurring in the kidney is glutamine metabolism, which initiates renal ammoniagenesis, central to the regulation of body acid-base homeostasis. The exact cellular processes enabling the tight and continuous regulation of ammonia production from glutamine must involve disposal of the carbon skeleton of glutamine molecules and the mechanisms of reoxidation of NADH which is produced as glutamine is metabolized and releases ammonia. The article by Drs. Patrick Vinay, Guy Lemieux, André Gougoux, and Mitchell Halperin provides their view on these aspects of glutamine metabolism based primarily on their own studies of the dog.

Because the renal tubular transport function is regulated and partly coupled with tubule cell metabolism, there may be derangements or adaptations in renal tubule metabolism as well as in renal tubular function in a variety of renal diseases. Drs. Saulo Klahr, Steven J. Schwab, and Thomas J. Stokes discuss some of the metabolic adaptations of the nephron which occur in renal diseases such as obstructive uropathy, acute renal failure, and chronic renal failure.

A variety of hormones, peptide, amine, steroid, thyroid hormones, and autacoids act on the kidney and play an important role in the delicate regulation of renal function. Some are even produced in the kidney and act as a local regulator of nephron function. Thus, the kidney is regarded not only as an excretory organ but also as an endocrine organ. A typical example is the fact that the kidney is the principal organ producing the active form of a steroid hormone, 1,25-dihydroxyvitamin D. The next four articles discuss certain endocrine aspects of renal function. Drs. Howard Rasmussen, Itaru Kojima, William Apfeldorf, and Paula Barrett provide their recent views on the mechanism of action of peptide hormones with particular emphasis on the role of the change in the flux of calcium ions across the plasma membranes, cyclic AMP, and protein kinase C. Their views, based mainly on recent observations in adrenal cells, have been somewhat modified from their own previous view on the subjects.

As noted above, the kidney is an essential endocrine organ for vitamin D activation. Dr. Hiroyuki Kawashima and I present our view on the sites and regulation of vitamin D activation, sites and mechanisms of action of 1,25-dihydroxyvitamin D, and effects of vitamin D on renal tubular handling of calcium and phosphate. Our view prompts questions on the interaction and physiological function of calcium regulating hormones, that is, parathyroid hormone, calcitonin, and 1,25-dihydroxyvitamin D in the kidney.

Two vasoactive hormonal systems in the kidney, prostaglandins and other arachidonate metabolites and kallikrein-kinin systems, are also discussed. Drs. Detlef Schlondorff and Raymond Ardaillou discuss recent advancements in autacoids research in the kidney. This chapter will be an excellent update of the previous *Kidney International* Symposium on "Prostaglandins and the Kidney," June, 1981.

Drs. A. G. Scicli and O. A. Carretero have contributed an excellent and lucid presentation on the kallikrein-kinin system in the kidney. They have added to the clarification of the analysis, the intrarenal localization, and the functional role of the system in the physiological and pathological conditions.

The final paper by Drs. Brian D. Ross, Dominique Freeman, and Laurence Chan is devoted to the application of nuclear magnetic resonance to the nephrology research and provides some interesting new observations and developments in this area of investigation. In particular, the technique may have highly useful clinical implications in acute renal failure, kidney preservation for transplantation, and characterization and proper chemotherapy of renal tumors.

Obviously, there is much more to be discussed in all the above-mentioned areas. A greater number of investigators should have been invited to contribute to this Symposium. However, the limitation of publication space did not allow us to do so. Also, we tried to avoid duplication of the topics which were discussed in the symposium issue, "Recent Advances in Renal Metabolism" in *Mineral and Electrolyte Metabolism,* edited by Dr. Richard L. Tannen and myself in 1983 [3]. In addition, there are, indeed, excellent recent articles on these and related topics [1, 2]. We sincerely hope the readers find this Symposium informative and provocative, and wish it may provide an impetus for future research in nephrology which will further narrow the boundary between physiology, biochemistry, and cellular and molecular biology. Finally, but not least, I would like to thank Drs. Roscoe R. Robinson, Editor Emeritus, and Thomas E. Andreoli, Editor, and all Associate Editors of *Kidney International* for providing me an opportunity to plan and work on the Symposium and for their advice, encouragement, and assistance in this endeavor.

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